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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	20

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/380,377	BULLEID, NEIL J	
	Examiner	Art Unit	
	Joseph Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED. (35 U.S.C. § 133)
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 March 2001*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,13-25 and 28-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,13-25 and 28-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☒ The proposed drawing correction filed on *9-16-99* is: a)☒ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
18)☐ Interview Summary (PTO-413) Paper No(s) _____
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other

DETAILED ACTION

This application is a 371 national stage filing of PCT/GB98/00468 filed 03/02/98, and claims priority to the foreign application 9704305.3 filed in the United Kingdom, 03/01/97.

The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claim 29 in supplemental amendment filed March 5, 2001 (paper number 19) has been renumbered 30.

The amendment filed January 9, 2001 (paper number 17), and supplemental amendment filed March 5, 2001 (paper number 19) have been received and entered. Claims 1, 3-11, 13, 14 and 16 have been amended. Claims 12, 26 and 27 have been canceled. Claims 29 and 30 have been added. Claims 1-11, 13-25 and 28-30 are pending and currently under examination.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible

harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-11, 13-22 and 28-30 are rejected under the judicially created doctrine of double patenting over claims 17-19 of U. S. Patent No. 6,171,827 since the claims, if allowed, would improperly extend the "right to exclude" already granted in the patent.

The subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming common subject matter, as follows:

The specification and claims of U.S. Patent 6,171,827 are drawn to a polypeptide comprising a pro-α collagen C-propeptide moiety with specific recognition sequences and a second moiety containing a triple helix forming domain (claims 1-11 and 14- 16) and a method of producing said polypeptides (claim 13). Also claimed is the DNA molecule encoding the polypeptides, an expression host cell and a method of producing collagen with said DNA and host cell (claims 17-19). The instant application claims a method of producing a desired procollagen by expressing in a host cell, a gene which encodes a polypeptide with the same embodiments recited in the claims

1-11 of U.S. Patent 6,171,827. Since the methods to produce the polypeptide in both applications are dependent on the broad claims encompassing any combination of procollagen chains, the claims 17-19 drawn to the polynucleotide encoding the desired procollagen polypeptide, the host cells expressing the polynucleotide and the method to produce a desired procollagen are the same as those recited in claims 1-11, 13-22 and 28-30 in the present application.

In the previous office action a provisional double patenting rejection was made over claims 1-22 and 28 and the same pending claims of then Application No. 09/029,348. See previous office action (paper number 15) page 3. Since the previous office action the pending claims of Application No. 09/029,348 which were part of provisional double patenting rejection have been allowed. In addition, claims 29 and 30 drawn the same subject matter have been added to instant application. Applicants argue that they do not agree with Examiner's position and have requested that the rejection be held in abeyance until the case in condition for allowance. See Applicants amendment (paper number 17) page 4. Applicants arguments have been fully considered but not found persuasive. The rejection is no longer a provisional rejection since the Application No. 09/029,348 has been issued as U.S. Patent No. 6,171,827.

Furthermore, there is no apparent reason why applicant was prevented from presenting claims corresponding to those of the instant application during prosecution of the application which matured into a patent. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11, 13-22, 28 stand rejected and claims 29 and 30 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing a desired procollagen polypeptide in a cell comprising; a) generating a polynucleotide which encodes a pro-α collagen chain polypeptide with altered selectivity for pro-α chain assembly comprising; i) a first C-terminal propeptide domain from a first pro-α chain type having activity for the assembly into a trimeric procollagen wherein said propeptide contains the recognition sequence GNPELPEDVL DVQLARLRLL SSR; and, ii) a second domain containing a triple helix forming domain from a pro-α chain type different from said first type, b) expressing said polynucleotide in a mammalian cell to produce said pro-α collagen chain polypeptide, and c) allowing said polypeptide assemble into said procollagen, does not reasonably provide enablement for a method of producing a procollagen with other specific recognition sequences other than GNPELPEDVL DVQLARLRLL SSR or in cells other than mammalian cells. The specification

does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Applicants argue that Examiner accepts that the specification is enabling for a method using a particular recognition propeptide however does not accept other examples of other sequences which can be used. See Applicants amendment, pages 4-5 bridging paragraph. Applicants arguments have been fully considered but not found persuasive.

The instant specification teaches specifically how one C-terminal domain can be used to assemble the trimeric domain of another procollagen molecule and gives specific guidance on how the specific amino acids in the C-terminal domain result in the recited recognition sequence of claim 6 (page 25). However, the specification is silent with respect to an example for the creation of other hybrid procollagens that demonstrates that the general strategy and the proposed recognition sequences of the other procollagen molecules will function as in the single detailed example.

As pointed out in Myllyharju *et al.*, experiments which demonstrate that expression of hybrid collagen molecules in insect and teach that wild type human procollagen can assemble in insect cells but is not stable unless human propyl 4-hydroxylase is also expressed (page 21824; middle of second column). Further, co-expression of proα1(I) and proα2(I) results in human type I procollagen, however,$[pro\alpha 2(I)]_3$ do not form (pages 21824-5; bridging paragraph). In Walmsley *et al.* the derivatives of collagen molecules derived from mini-genes absent of triplex forming regions, can be created and expressed, however the polypeptides encoded by these mini-

genes will not assemble in procollagen molecules (page 14891; top of column 2). Therefor, by extension, not all possible derivatives of procollagen can be used to direct the formation of a desired collagen molecule. Applicant has proposed a potential method for the assembly of procollagen molecules, however, because the assembly of collagen is a complex multi-step process, modifications to the endogenous gene may result in modifications which would produce a hybrid molecule incapable of producing the desired collagen. The claims encompass generation any desired collagen molecule and encompass the use of any combination of C-terminal domain with any trimeric forming domain for the assembly of the desired procollagen. Further, the breadth of the claims encompass the assembly of trimeric domains of different species through the use of the C-terminal propeptide domain and the use of any type of cell from any species for the assembly of procollagens from any species. Applicants have described a potential method for the assembly of desired collagen molecules and prophetic recognition sequences based on computer homology searches, however for the reasons detailed above without the reduction to practice of more than one example, it is not clear if the predicted methodology will be operative for all the different combinations of collagen molecules encompassed in the scope of the claims. Further, Applicants have not addressed the problem of the extensive post-translational modification of collagen molecules and the need of other enzymes, such as the propyl 4-hydroxylase in yeast, to obtain a collagen molecule which would assemble properly, and so have not provided the proper guidance to achieve the proposed method in all types of cells.

Thus, in view of the of the lack of guidance, working examples, breadth of the claims, skill in the art and state of the art at the time of the claimed invention, it would require undue experimentation by one of skill to practice the invention in the breadth in which it is claimed. Therefore, for the reasons above and of record the rejection is maintained.

JW 5/7/01 Claims 23-~~26~~ 25 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

JW 5/7/01 Claims 23-~~26~~ 25 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants argue that the technology necessary to practice the claimed invention would be considered standard and in support of the ability to generate a transgenic animal or plant have submitted a post filing paper by David *et al*. See Applicants amendment bottom of page 5 and attached manuscript. Applicants arguments have been fully considered but not found persuasive.

Examiner agrees that the methodology to create a transgenic mouse and a transgenic plant are becoming routine in the art, however, these arguments are not deemed persuasive because the central issue is whether Applicants were in possession of the claimed animal without actually having made such an animal. As presented in the previous office action (see pages 8-12 and 15-18), the phenotype of a transgenic animal can not be predicted because the art of transgenics is unpredictable due to the behavior of the inserted transgene construct. The question then is, can one skilled in the art envision the distinguishing characteristics of the claimed animals without an actual reduction to practice. Applicants have not provided arguments or pointed to support in the specification to demonstrate that one skilled in the art could distinguish the claimed transgenic animal from a normal animal. While Applicant is correct in the assertion that the creation of a transgenic mouse is becoming routine to one skilled in the art, the art recognizes that production of a transgenic mouse depends on the site of integration of a transgene as well as the number of the copies integrated in the genome of the transgenic mouse. Furthermore, the effects of expression in different lines of mice, as well as in variation of expression in different tissues due to the use of different promoters may not be predicted due to the level of the production of the transgene. Specifically, as pointed out in the previous office action, Berg teaches that a single procollagen can be expressed in a transgenic mammal wherein the animal is essentially a bioractor and the collagen produced is assembled and secreted. However, because the specification does not disclose the details of expressing the procollagen chain, the expected effect of introducing the nucleic acid, nor if/what cellular material it expects to modify, the claims encompass changes

which may produce an animal which is not viable or incapable of producing progeny. In particular, read in light of the specification, one embodiment is the production of heteromeric collagen chains between species which has presently not been demonstrated in art. As taught in the specification, the proposed mechanism for nucleation and assembly of procollagen chains can be found in the C-terminal propeptide portion of the procollagen chain (pages 27-28; bridging paragraph), however, as demonstrated in Colombatti *et al.* when intact genes for procollagen are expressed in non native host cells, in this case chicken procollagen in mouse NIH3T3 cells, no self-association was observed for either α1(VI) or α2(VI) (page 785; summarized in abstract) suggesting that not all combinations of procollagen chains will undergo the proper processing and/or assembly in any type of cell. Furthermore, because of the lack of homology of procollagen chains between species, the α1(VI) or α2(VI) from chicken do not form the chimeric chicken/mouse heteromers one expected based on known structures and homology, suggesting further that domain switching between procollagen chains will not result in the formation of any and all combinations of desired procollagen chains (page 785; summarized in abstract). A more general illustration of the inability to predict a phenotype was given by Hammer *et al.* who report the production of transgenic mice, sheep and pigs; however, only transgenic mice exhibited an increase in growth due to the expression for the gene encoding human growth hormone (pages 276-277, Subsection: Effect of Foreign GH on Growth). With respect to transgenic plants, Ruggiero *et al.* demonstrate that one can express the proalpha1(I) chain in plants, however, it not clear that expression of other procollagen chains, and in particular the hybrid genes recited in the

claims, will be expressed, processed and assembled properly in a plant host. Therefore, because there is no evidence that any claimed animal or plant was made at the time of the claimed invention, and because one skilled in the art could not predict or envision any distinguishing features of the claimed transgenic animals or plants, there is no evidence of record that Applicants were in possession of any of the claimed animals or transgenic plants.

Thus, in view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to practice the invention as claimed. Therefore, for the reasons above and of record the rejection is maintained.

Claims 26 and 27 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is withdrawn.

Applicants have canceled claims 26 and 27 rendering the basis of the rejection moot.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11, 13-25, 28-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

Claims 1 and 30 are incomplete because they recite a method for producing a desired procollagen in a system, however the claims does not recite any method steps to this end only embodiments of the desired procollagen or system. Dependent claims 2-11, 13-25, 28 and 29 are included in this rejection because they fail to clarify the basis of the rejection in the independent claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.
>
> (f) he did not himself invent the subject matter sought to be patented.

Claims 1, 2, 6 and 11, 13-22 stand rejected and claim 29 is newly rejected under 35 U.S.C. 102(a) and 35 U.S.C. 102(e) as being anticipated by Prockop *et al.*

Applicants argue that the Prockop *et al.* simply does not teach the claimed subject matter. See applicants amendment, page 6. Applicants arguments have been fully considered but not found persuasive.

Newly added claim 29 encompasses the method according to claim 21 wherein the cell is a mammalian cell. As pointed out in the previous office action, Prockop *et al.* teach hybrid pro-collagen genes which encode hybrid polypeptides (column 2; lines 25-57), specifically, the 5' COL1A1 encoding a portion of the pro-α1 type I chain is linked to the COL2A1 gene which encodes the pro-α1 type III chain. Further, Prockop *et al.* provide the guidance and teach the necessary steps for a method in which the recombinant procollagen polynucleotides can be expressed in yeast (columns 12-14; Examples 8-9), insect cells (columns 10-12; Example 7) and **mammalian cells** (column 7-10; Examples 1-6) to produce the desired pro-α collagen chains and/or assembled procollagen in these cells. Finally, Prockop *et al.* specifically teach that one can express multiple copies of the gene and that one can engineer sites to produce "desired regions of procollagen or collagen" (column 10; lines 52-56). The recognition sequence recited in claim 6 of the present application is the same sequence present in COL2A1 gene which encodes the pro-α1 type III chain taught in Prockop *et al.* Embodiments encompassed in claims 11-16 are taught throughout the specification in particular at column 10; lines 52-56.

Therefore for the reasons above and of record, Prockop *et al.* anticipate the claimed invention, and the rejection is maintained.

Claims 1-11, 13-22 and 28-30 are rejected under 35 U.S.C. 102(e) as being anticipated by Bulleid *et al.* (US Patent No. 6,171,827).

In the previous office action a provisional 35 U.S.C. 102(e) rejection was made over claims 1-22 and 28 and the same pending claims of then Application No. 09/029,348. See previous office action (paper number 15) pages 20-21. Since, the previous office action the pending claims of Application No. 09/029,348 which were part of provisional rejection have been allowed. Further, based upon the earlier effective U.S. filing date of the copending application 09/029,348, now Patent No. 6,171,827, it would constitute prior art under 35 U.S.C. 102(e), if patented. Applicants argue that the disclosure of Bulleid *et al.* does not teach the claimed subject matter. Applicants arguments have been fully considered but not found persuasive.

As noted in the nonstatutory double patenting rejection above, the specification and claims of U.S. Patent 6,171,827 are drawn to a polypeptide comprising a pro-α collagen C-propeptide moiety with specific recognition sequences and a second moiety containing a triple helix forming domain (claims 1-11 and 14- 16) and a method of producing said polypeptides (claim 13). Also claimed is the DNA molecule encoding the polypeptides, an expression host cell and a method of producing collagen with said DNA and host cell (claims 17-19). The instant application claims a method of producing a desired procollagen by expressing in a host cell, a gene which encodes a polypeptide with the same embodiments recited in the claims 1-11 of U.S. Patent 6,171,827. Since the methods to produce the polypeptide in both applications are dependent on the broad claims encompassing any combination of procollagen chains, the claims

17-19 drawn to the polynucleotide encoding the desired procollagen polypeptide, the host cells expressing the polynucleotide and the method to produce a desired procollagen are the same as those recited in claims 1-22 and 28-30 in the present application.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen M. Hauda, can be reached at (703)305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist Kay Pickney whose telephone number is (703)306-3076.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

Joseph T. Woitach

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER